# SDS AFFECTS THE PHYSICOCHEMICAL PROPERTIES OF PVA-STABILIZED SOLID TRIGLYCERIDE NANOPARTICLES

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## ABSTRACT

Solid triglyceride nanoparticles are under intensive investigation as drug delivery systems. In the solid state, triglycerides exist in three polymorphic modifications which differ from each other in their physicochemical properties. Thus, it is particularly important to know the influence of parameters affecting the polymorphic behavior of the solid triglyceride nanoparticles to get a stable product with defined physicochemical properties over an appropriate storage time. This study investigated the effect of subsequent addition of SDS to tripalmitin nanoparticles, which had been stabilized with partially hydrolyzed poly(vinyl alcohol) (PVA). The polymorphic behavior was characterized with DSC and X-ray diffraction over a storage time of 28 d at 20 °C. A faster transition into more stable polymorphic modifications was observed after the addition of SDS to the nanoparticles.

*Keywords: triglycerides, polymorphism, PVA, SDS*

## INTRODUCTION

Nanoparticles of solid lipids were first investigated by Speiser et al. [1986] and further developed as potential drug delivery systems for poorly water-soluble drugs [Bunjes, 2010]. The physicochemical properties of the nanoparticles depend on, e.g., the used matrix lipid, the stabilizer as well as additional substances. As matrix lipid e.g., triglycerides can be used. Triglycerides are polymorphic substances and mainly occur in three different polymorphic modifications. These modifications differ from each other in their physicochemical properties due to a different arrangement of the triglyceride molecules [Chapman, 1962]. According to Ostwald's step rule, triglycerides crystallize in the metastable α-modification and undergo time- and temperature dependent monotropic transitions into the stable β-modification, sometimes via the β'-modification. The different physicochemical properties of the solid triglyceride particles when present in different crystal modifications might influence the drug loading capacity as well as the physical stability of the dispersion. Therefore, it is essential to understand the effect of additives to obtain a stable product over the necessary shelf life. In this study, tripalmitin was used as matrix lipid and the nanoparticles were stabilized with partially hydrolyzed poly(vinyl alcohol). SDS was added to the dispersions to investigate the effect on the physicochemical behavior of the PVA-stabilized nanoparticles and to get further information about how PVA interacts with the matrix lipid.

## RESEARCH CONCEPT

For this study, dispersions consisting of 5 % tripalmitin (Dynasan® 116, Condea), 5, 7.5, 10 or 15 % Kuraray Poval 3-83 (Kuraray Europe GmbH) and bidestilled water, in which the PVA was dissolved, were prepared by high pressure melt homogenization (all concentrations w/w). To each dispersion 0.1 or 0.3 % SDS (Carl Roth GmbH) was added after the homogenization procedure as described in this section. A dispersion without SDS was used as reference.

First, the lipid and the aqueous phase were heated at approx. 80 °C separately. Afterwards, both phases were combined and pre-homogenized with an ultra-turrax (IKA T25 digital Ultra-Turrax; SN25-10G, IKA-Werke) at 13.000 rpm for 4 min. The premix was homogenized in a preheated Microfluidizer M110-P instrument (Microfluidics) for 10 cycles at 800 bar. The hot dispersion was divided into three parts. To two parts

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SDS in the respective concentration was added as a powder in the heat and dissolved under gentle shaking. In a following cooling step, the matrix lipid was allowed to crystallize in an ice-water bath.

The particle size was measured with a Zetasizer Nano ZSP instrument (Malvern) at 25 °C and an angle of 173 °. The dispersions were diluted with purified and particle free water. The z-average diameter and PDI were given as mean of three measurements of 5 min each after 5 min of equilibration.

Differential scanning calorimetry (DSC) measurements were performed in a DSC 3 Star$^e$ System with a full range sensor (FRS 6+) and a sample robot (Mettler Toledo GmbH). 15 µl of the dispersions were accurately weighed into aluminum crucibles that were cold sealed. The samples were heated from 0 to 85 °C with a heating rate of 10 K/min, held at that temperature for 10 min and cooled to -5 °C with a cooling rate of 10 K/min. As a reference, an empty aluminum pan was used, and all measurements were performed under nitrogen purge. The enthalpies obtained as areas under the curve upon evaluation were normalized for the weight of the samples.
The melting enthalpies were used to approximate the formation of particles in the stable β-modification.

X-ray measurements were performed with a small- and wide-angle X-ray diffraction setup (SAXSess mc², Anton Paar) equipped with a copper radiation source (λ = 0.154 nm) and a CCD detector as well as a Mythen detector. The sample was measured in a quartz capillary sample holder in 20 runs of 60 s each at 20 °C. Background subtraction and desmearing was performed for all diffractograms.

## RESULTS

All dispersions had a milky white appearance. However, the more PVA was used as emulsifier, the more transparent was the dispersion. After the addition of SDS, the appearance did not change. The z-average and PDI values were 75 - 100 nm or 0.10 - 0.20, respectively, and depended on two parameters. First, the more PVA was used, the smaller were the particles. Second, with addition of SDS the z-average and PDI values increased. This effect on the particle size was less pronounced when more PVA was used in the original dispersion.
During cooling the sample in the DSC, the crystallization temperature increased with the addition of SDS from approx. 25 to 28 °C for tripalmitin

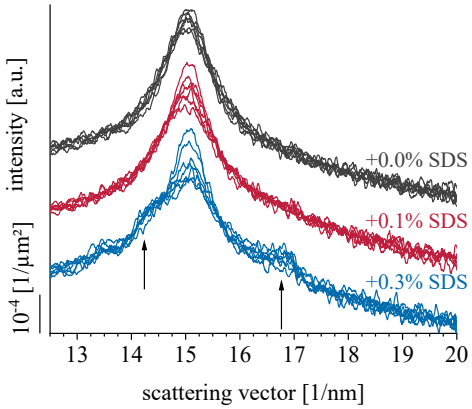


**Figure 1**: Wide angle X-ray diffractograms of tripalmitin nanoparticles. The composition of the dispersions was 5 % tripalmitin, 5 % Kuraray Poval 3-83 and 0, 0.1 or 0.3 % SDS, respectively. The diffractograms were recorded after 0, 1, 4, 7, 14, 21 and 28 d of storage at 20 °C.

nanoparticles, which were stabilized with 5 % PVA. Comparable to the effect on the particle size, the influence on the crystallization temperature also decreased with increasing total PVA concentration in the sample. In this case, the crystallization temperature was nearly constant at 22 °C for dispersions, which were stabilized with a total PVA-concentration of 15 %.
After crystallization, all particles were present in the metastable α-modification, which was confirmed with DSC and X-ray measurements. According to the SAXS patterns, the triglyceride in the lipid particles was arranged with a reduced lamellarity. The SAXS signals increased over the storage time for all samples. The 0.3 % SDS-containing sample displayed additional signals in the wide-angle scattering pattern at approx. 14.2 and 16.8 $nm^{-1}$ (fig. 1). During the observed period of storage, the matrix lipid underwent time-dependent polymorphic transitions into more stable modifications. This could be confirmed with DSC measurements, which showed an increased size of the melting event at higher temperatures after 28 d of storage.
In contrast, there were no indications for the presence of particles in the β'-modification in the wide-angle range of the sample without SDS (fig. 1). These effects were also observed for the dispersions stabilized with higher concentrations of PVA or only 0.1 % additional SDS.

## DISCUSSION

The addition of SDS to tripalmitin nanodispersions stabilized with partially hydrolyzed PVA had an

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influence on their physicochemical behavior. It is known that PVA has a strong stabilizing effect on metastable polymorphic modifications in triglyceride nanoparticles [Rosenblatt et al., 2008]. The assumption in the present study was that the stronger the interaction between PVA and the matrix lipid, the lower is the crystallization temperature and the higher the stability of the metastable α-modification. The increase of the crystallization temperature with increasing SDS concentration might be an indication that the interaction between the matrix lipid and PVA is weakened in comparison to the reference dispersion without SDS.

Another indication for the reduction of the interaction between the matrix lipid and the main emulsifier, PVA, is the more pronounced polymorphic transition into more stable modifications. The particles with SDS addition transformed more rapidly into the β'-modification, which could be detected in the WAXS-pattern in fig. 1 [Chapman, 1962].

A possible cause of the observed phenomena might be an interaction between PVA and the additional SDS, which might influence the stabilization properties of PVA. It is supposed that SDS associates with PVA thus leading to a stretching of the polymer [Ramirez, 2020]. This could cause a more hydrophilic character of PVA. Consequently, the interaction between PVA and the matrix lipid would be reduced, which is reflected in the increasing crystallization temperature of the triglyceride nanoparticles.

The higher the PVA concentration, the lower is the effect of SDS addition on the observed effects on the crystallization temperature as well as on the particle sizes and the polymorphic behavior of the solid triglyceride nanoparticles.

This concentration dependent effect could be due to the relatively low SDS concentration in comparison to the high PVA concentration. Possibly, the SDS concentration is not high enough to exhibit a major effect on the high number of PVA molecules, which are located at the particle surface, or is preferably associated with free PVA molecules, which are assumed to be present in the aqueous phase.

There were no clear indications that SDS acts as main stabilizer by adding it after homogenization. A particularly prominent indication that PVA was still the main stabilizer is the less ordered structure of the particles after crystallization, which was not observed for SDS-stabilized triglyceride particles [Bunjes et al., 2002].

## CONCLUSIONS

This study indicated that PVA-stabilized solid tripalmitin nanoparticles can undergo polymorphic transitions into more stable modifications more easily after the addition of SDS. This knowledge is important for the estimation of the stability of the product as potential drug delivery system. Furthermore, the addition of SDS might contribute to a better understanding of how PVA physically stabilizes the triglyceride nanoparticles and induces such a high stability of the metastable α-polymorph.

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